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French title: Localiser le diagnostique prénatal non invasif: les pratiques et les significations des tests fondés sur l'analyse de ADN fœtal dans le sang de la mère en Chine, Italie, Brésil et le Royaume Uni

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English Abstract

This paper is the result of a collaborative work between researchers based in UK, Italy, China and Brazil, and aims at providing a comprehensive review of practices and meanings of Non-Invasive Prenatal Testing (NIPT) in these countries, while also highlighting the ethical implications that NIPT poses. In the first part of this paper we describe how the technology is being integrated into the 'moral economy' of prenatal testing in the different countries we analysed. The uses of NIPT differ greatly in the countries we analysed.

In the second section of the paper we position NIPT within the trajectory of prenatal diagnosis that, displays the role of conflicting values and often incommensurable moral economies in the emergence of new technologies, and in their transformation into routine medical procedures. The two 'often incommensurable moral economies' are women's autonomy and individual-centred medicine, as emphasised in gynaecologists and midwives/obstetricians' public discourse; and considerations about the cost/efficacy of long-term care for people with Down Syndrome or other chromosomal-related disabilities as emphasized in public health discourses. We discuss how these two contrasting narratives are also at play (more or less covertly) in the discourses around NIPT. We then consider some of the ethical issues raised by NIPT, including the argument that NIPT will lead to a harmful bias towards people with Down Syndrome and to an increase in termination rates; and the ethical issues raised possible incidental findings resulting from a maternal chromosomal mosaicisms due to an anomalous cellular line, and other hidden abnormalities in one of the parents, including genetic diseases with late expressions in life. We note how the counselling step following incidental finding will be of the utmost importance and that in many countries, including the ones we analysed, doctors and healthcare professionals are not adequately prepared for it. We conclude that it is important that bioethics scholarship engages proactively with the ethical issues that arise at the nexus of these conflicting values and moral economies, especially as future evolutions of NIPT combined with whole genome sequencing (WGS) will affect women's reproductive decisions, and shape the scope of their reproductive choices, in a way that will lead to a completely new level of 'supervision', 'management' and 'scrutiny' of human foetuses and pregnant women.

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French key-words (Mot-clefs): diagnostique prénatal, tests prénataux non invasifs, NIPT, maladie génétique

French Abstract

Cet article est le résultat d'une collaboration entre des chercheurs qui ont étudié l'évolution du diagnostique prénatal au Royaume Uni, en Italie, en Chine et au Brésil. Il passe en revue les pratiques liées à l'introduction des tests prénataux non invasifs (NIPT) dans ces pays, et discute les questions éthiques liées à l'introduction de cette nouvelle approche diagnostique. En Chine, en Italie, au Royaume Uni et au Brésil le NIPT est déjà présent sur le marché. Toutefois, bien que la technologie utilisée pour analyser l'ADN fœtal dans la circulation maternelle soit bien établie et semblable partout, et que tous les producteurs commerciaux de NIPT proposent des services équivalents, les trajectoires situés de cette nouvelle approche diagnostique ont été très différents. Ceci n'est nullement étonnant. Les applications d'une technologie biomédicale sont toujours situés, et dépendent du contexte social, culturel, économique et politique dans lequel elle est introduite.

La première partie de ce texte décrit l'intégration du NIPT dans les structures préexistantes du diagnostique prénatal dans chacun des pays étudiés. Le 18 Janvier 2016 le comité national chargé des tests de dépistage au Royaume Uni (UK National Screening Committee) a constaté que le NIPT prédit avec précision la présence du syndrome de Down (trisomie 21), du syndrome d'Edwards (trisomie 18) et du syndrome de Patau (trisomie 13), et a recommandé que le NHS (National Health Service) diffuse le NIPT pour ces trois conditions. De toute vraisemblance, en 2017 ou 2018 ce test sera proposé à toutes les femmes enceintes au Royaume Uni, indépendamment de leur risque d'avoir un enfant trisomique. Les medias et certains experts ont argumenté que la mise en oeuvre du NIPT au Royaume Uni à travers le NHS va produire une véritable révolution du diagnostique prénatal. Nous proposons, par contre, que de toute vraisemblance cette démarche va conduire à une 'modulation' plutôt qu'à une 'révolution', des pratiques du diagnostique prénatal.

En Italie plusieurs groupes régionales et nationales sont en train d'évaluer la possibilité d'introduire le NIPT dans le système de santé national. En Chine, en décembre 2015, le NIPT a été inclus dans le système public de soins anténataux de la ville de Shenzhen (une ville de plus de 10 millions d'habitants) , la première ville chinoise à faire ce choix. A Shenzhen, les femmes enceintes payent 88RMB (environs 115 euros) pour le NIPT; le restant du prix de ce test (plus que la moitié) est couvert par les services de santé de Shenzhen. En Chine, le NIPT détecte uniquement des aneuploïdies; la détection du sexe du fœtus est strictement interdite, pour empêcher un avortement sélectif des filles. Au Brésil l'avortement pour une indication fœtale est interdit (avec la seule exception de l'anencéphalie) et le système national de santé (SUS, Sistema Unico de Saude) n'offre pas de diagnostique prénatal. Toutefois, les femmes des classes moyennes et supérieures utilisent exclusivement les services de santé privés, et ont accès aux tests prénataux et à l'avortement (illégal) pour une indication fœtale. Le NIPT a été aisément intégré à ce système privé de soin. Une particularité du système brésilien est une diffusion large des tests, fondée sur l'analyse de l'ADN fœtal dans le sang de la mère, qui détermine précocement le sexe du fœtus. Ces tests, relativement peu onéreux, ont comme but d'intégrer le futur enfant dans la famille. Ils ne sont pas liés aux

avortements sélectifs, puisque les brésiliens n'ont pas une préférence forte pour des enfants d'un sexe déterminé.

La deuxième partie de cet article discute les problèmes éthiques soulevés par l'introduction du NIPT. Notre hypothèse est que l'effet principal de la généralisation du NIPT sera probablement une diminution drastique du nombre de tests invasifs : l'amniocentèse et la biopsie des trophoblastes. Une autre conséquence potentielle sera un diagnostique plus précoce des anomalies fœtales; ceci peut dans certains cas favoriser la décision de terminer une grossesse. Nous doutons néanmoins que la diffusion du NIPT va augmenter le nombre d'avortements pour des indications fœtales. L'introduction du NIPT ne va probablement pas changer d'une manière considérable le taux d'interruptions de grossesses pour trisomie 21, puisque dans la majorité des cas cette condition est déjà détecté avant la naissance par d'autres moyens. Le NIPT ne va probablement pas non plus induire une hausse importante d'avortements pour d'autres indications fœtales. Les craintes que les femmes allaient avorter pour des raisons 'triviales' ou pour des handicaps 'mineurs", fréquemment exprimées après la légalisation de l'avortement en Europe et en Amérique du Nord dans les années 1960 et 1970, ne se sont jamais matérialisées. Il semble donc peu probable que le NIPT va favoriser l'explosion de tels avortements. Toutefois, cette supposition n'est pas fondée sur des données empiriques. Il sera désirable d'accompagner la diffusion large du NIPT par un suivi des décisions de femmes qui ont appris la présence d'une anomalie fœtale par ce test. Il sera aussi désirable de suivre les conséquences de la révélation accidentelle des problèmes maternels/parentaux par le NIPT, tel le mosaïsme cellulaire chez la femme enceinte, ou la présence d'une maladie génétique dans la famille; de telles révélations accidentelles sont un des problèmes éthiques les plus épineux liés à la généralisation du NIPT. Les femmes qui reçoivent un tel diagnostique accidentel ont un besoin urgent de conseil génétique de qualité, mais la majorité des médecins qui prescrivent le NIPT ne sont pas formés pour le fournir. En outre, quand le NIPT est distribué par des compagnies privées et pas par un service de santé national, il y a un risque considérable que ce test soit administré dans des centres qui ne sont pas équipés pour assurer un suivi approprié des femmes testés.

La conclusion de l'article discute l'intégration du NIPT dans un ensemble de tests prénataux. Ces tests reflètent des valeurs contradictoires. Les médecins libéraux mettent en avant la nécessité de respecter l'autonomie des femmes et des couples, tandis que les spécialités de la santé publique avancent des considérations relatives au cout monétaire, social et émotionnel des soins d'individus ayant des problèmes graves de santé. Malgré l'existence d'importantes tensions et contradictions autour du diagnostique prénatal, les technologies utilisées pour surveiller le développement du fœtus sont devenus des tests médicaux de routine. Ceci va probablement être également le devenir de NIPT. Notre article évoque brièvement aussi des futurs possibles pour le NIPT, avant tout la prédiction que cette technologie sera bientôt couplée avec le séquençage complet du génome (Whole Genome Sqeuencing, WGS). Un tel développent rendra le fœtus encore plus accessible au regard des médecins, et augmentera considérablement les possibilités de surveillance et de contrôle des futurs êtres humains, mais aussi des femmes enceintes. Il est donc très important de commencer dès maintenant un débat publique sur les dimension éthiques d'une telle évolution, et d'inclure dans un tel débat le point de vue des usagers, avant tout celui des femmes.

1. Introduction

This is a fascinating time to discuss the changing landscape of prenatal testing. On January 18th, 2016 the UK National Screening Committee reported evidence that Non-Invasive Prenatal Testing (NIPT) is highly accurate for detection of foetal chromosomal aneuploidies (the presence of an abnormal number of chromosomes) including the detection of Down syndrome (trisomy 21), Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13), and recommended it for implementation through the National Health Service (NHS) in substitution of invasive screening. In Italy, from January 2016 a private company (Genoma Group) is the first to offer NIPT not only to detect the trisomies above but also for any aneuploidy and structural chromosomal alterations (deletions and duplications) on each chromosome. In Brazil, the NIPT market has flourished among the upper-middle class in the last three years and offers testing mainly for sex-determination. To the contrary, China, which had offered NIPT since 2011, put a hold to all testing in February 2014 because of what was perceived as an unregulated and chaotic commerical market. Since June 2014 NIPT has been offered again for aneuploidies in the province of Shenzen, but not for the detection of fœtal sex which remains strictly prohibited

Commercial companies in many countries worldwide, including the UK, China, Italy and Brazil already offer NIPT. In the first years since its introduction, NIPT has been promoted as an upscale product, one of the components of a 'quality pregnancy care' available to affluent women able to pay for this test out of their pocket [1]. This is what currently happens in Italy and the UK, and in some parts of China too. Such a use of NIPT in a 'middle income' country like Brazil is not self-evident. In such countries, NIPT can be mobilised to improve women's access to prenatal diagnosis, especially outside urban centres. Blood samples of pregnant women can be taken by community health workers and sent to central laboratories, reducing the need for professionals to perform invasive procedures and interpret tests results. Such a scenario assumes, however, a willingness to diffuse prenatal testing and, implicitly, a possibility to abort impaired foetuses. Neither exists in Brazil, where NIPT has become a 'status symbol' for upper-middle class that uses it mainly for sex-determination early in the pregnancy, as described below.

It is often read that the expected implementation of NIPT through the public health system in the UK and in other countries including Italy in the near future promises to 'revolutionise' the landscape of prenatal testing. But, as we argue in this paper, in the near future the implementation of NIPT through the national health system will lead to a 'modulation', instead than a 'revolution' of the landscape of prenatal testing.

This paper is the result of a collaborative work between researchers based in UK, Italy, China and Brazil, and aims at providing a comprehensive review of practice and policy

landscapes in these countries, while also highlighting the ethical implications that NIPT pose. As the technology is relatively simple and inexpensive, but with manifold and culturally- dependent applications, it is important to discuss at an early stage how NIPT is changing the landscape of prenatal testing and point to some areas in need of ethical attention.

2. How NIPT is changing the landscape of prenatal testing

NIPT and non-invasive prenatal diagnosis (NIPD) are techniques based on the analysis of maternal cell free foetal DNA (cffDNA). The year 1997 marked a milestone for NIPT/NIPD, when cffDNA was found in maternal plasma. cffDNA originates mainly from the placenta, and is constituted by 150-200 base pair fragments which are released in the mother's blood, where it is first detectable at about 4-5 weeks of gestation. At about 10 weeks, the concentration of cffDNA reaches the sufficient level for NIPT [2]. The reports released in 2008 by two independent research groups of the successful non-invasive diagnosis of foetal aneuploidy by using massively parallel genomics sequencing of cffDNA in maternal plasma [3,4] marked the real breakthrough of NIPT. In these two studies, statistics was used to diagnose the foetal aneuploidy. Both teams found out that the percentage of cffDNA in the maternal plasma averages around 10%. Assuming that the concentration of cffDNA is 10% of maternal plasma, a given range of plasma contains 90 units from mother, 10 units from the foetus. While normally in pregnancy the total quantity of chromosome 21 should be 200 units (mother's chromosome 21 is 90 units * 2, and the foetus' is 10 units *2), in case of trisomy 21 (Down syndrome) 210 units are counted of the total quantity of chromosome 21, as there are 10 additional units from the foetus. The detection of foetal aneuploidies (chromosomal abnormalities in terms of numbers, or structural rearrangements) is usually performed through invasive cytogenetic tests through chorionic villus sampling (CVS) at weeks 13+ 6 weeks, or amniocentesis from 15+0 weeks.

NIPT is defined as 'non-invasive' exactly in contrast to CVS or amniocentesis, which pose a risk of miscarriage of about 0.5-1% [5]. NIPT is not a diagnostic test, as it requires invasive test confirmation through either CVS or amniocentesis to confirm the diagnosis of a chromosomal aneuploidy. However, as explained in more detail below, the accuracy of the test has been constantly improving, and is now very similar to the accuracy of the invasive tests. As such, it is not implausible to speculate that in the future NIPD could be elevated to a diagnostic test, and will nearly completely substitute invasive testing, at least for some applications (there is a false positive rate which would still require confirmation through invasive screening).

In Italy, where one of the authors (Zannoni) is gynaecologist working in a university research hospital in the Emilia-Romagna region in northern Italy, NIPT is offered by private companies for a median price of € 571. Regional working groups are being formed to evaluate NIPT and then formulate recommendations on the use of NIPT within the current prenatal testing system for the diagnosis of foetal chromosomal aneuploidies (trisomies 13, 18, and 31) and aneuploidies of sexual chromosomes.

Currently all women in Italy are offered a combined test through the SSN (Sistema Sanitario Nazionale, equivalent of the NHS) to determine the risk of foetal aneuploidies. The combined test determines the risk of foetal aneuploidies through an algorithm [6] that combines: a) the maternal age, b) the values of two serum markers (maternal serum pregnancy-associated plasma protein A, PAPP-A, and maternal serum Beta human chorionic gonadotrophin, beta-hCG) measured between 10+0 and 14+1 weeks of gestations, and c) the value of nuchal translucency measured with a scan at 11+2 and 14+0 weeks of gestation. The combined test offers an estimate of the individual probabilities of carrying a foetus affected by trisomy 13, 18 or 21. In addition the combined test can offer some indications to determine other congenital anomalies, such as cardiac malformations [6]. The estimate of each individual probability is compared with a pre-established cut-off (usually 1/250 in Italy, but much lower in UK and China, about 1/150): if the probability is below 1/250, the result of the combined test is considered negative; if the probability is above 1/250, the result of the test is considered positive, in which case the woman is offered the possibility to undergo an invasive cytogenetic test (CVS or amniocentesis) to confirm the result of the test.

Compared to the combined test, NIPT testing has at least two advantages as it becomes better able to provide a more accurate estimate of the risk of trisomies 13, 18, and 21. There is increasing evidence that a higher accuracy detection rate has been achieved with NIPT compared to the current DSS [7-10]: 99.2% for T21, 96.3% for T18 and 91% for T13. This in turn leads to a reduction in the number of false positives, and of the number of invasive tests that need to be carried out, with subsequent reduction in the risk of miscarriage which is inherent in the invasive tests, and a reduction of costs on the national health system [1]. The second advantage is that NIPT offers a calculation of risk of foetal aneuploidies at an earlier stage in pregnancy. The assumption here is that earlier testing potentially reduces stress for the woman in the case of a positive test. Since early in a pregnancy the woman would be less emotionally attached to the foetus, then if the woman decides not to continue the pregnancy an abortion would be less emotionally stressful (with the noted exceptions of course of a pregnancy considered to be 'precious' e.g., if the woman is having difficulties to conceive, or for other emotional reasons). In addition, the risk of spontaneous miscarriage is much higher in the first trimester when NIPT is

performed, and of course it should not be discounted that the implementation of NIPT would be less burdensome on the national health system.

In Italy invasive cytogenetic tests are offered free of charge through the SSN to all women older than 35 years of age; women with previous children affected by chromosomal abnormalities; in case of one parent with structural chromosomal rearrangement not associated with any phenotypic effect and; in case of anatomical anomalies detected at scanning; or in case of positive result of combined test. Compared to traditional invasive cytogenetic tests, such as CVS or amniocentesis, NIPT is able to detect 92 % of foetal chromosomal anomalies which are detectable prenatally, and 96 % of foetal chromosomal anomalies detected at birth (the discrepancy between the two being due to the fact some pregnancies with malformations do not result in the birth of a viable child), reaching a level of detection rate very similar to the one of traditional foetal karyotyping (the characterization of an individual's chromosomal complement) obtained with invasive cytogenetic testing of 96.9%[1]. In addition, compared to invasive cytogenetic tests, NIPT testing would not only offer the advantages of being non-invasive and being offered earlier on in the pregnancy, but would also avoid some of the critical care and emergency (urgent) situations that are frequent in the traditional invasive diagnosis. These critical care instances are not only distressful for the woman, but pose also a cost to the national health system.

It is important to note at this point that, even in the case in which NIPT were offered to all pregnant women, it would not substitute completely the combined test, as the latter as mentioned above also offers information on the risk of cardiac malformations, which would not be captured by the NIPT. For these reasons it should be recommended that blood sampling for NIPT should be always associated with a first trimester scan with nuchal translucency evaluation.

It is also important to note that the NIPT results could be affected by other factors that do not affect the combined test, resulting possibly in false positive, or in incidental findings related to the mother. These are:

a) Maternal constitutional mosaicisms: as NIPT is performed on maternal and foetal DNA, there could be an anomaly in the chromosomal karyotype of the mother, for example due to an anomalous cell line of the mother non necessarily linked to any phenotypical anomaly [11]
b) Maternal chromosomal anomalies of iatrogenic origin (non-constitutional): similarly the result of the test can be compromised by the presence in the blood of mutated DNA fragments from the mother caused by pharmacological, physical, or viral agents that can damage DNA

[1] http://www.salute.gov.it/imgs/C_17_pubblicazioni_2381_allegato.pdf (accessed April 4th, 2016)

c) Vanishing twin: in case of a twin pregnancy in which one of the two twins was spontaneously interrupted this could result in fragments from placental DNA of an aborted foetus in the first few weeks [12]

Both one and two can not only compromise the result of the test (potentially leading to a false positive result) but also raise ethical issues, as they could involve uncovering hidden anomalies in a parent(s) and their families, including potentially an abnormal cell line which can indicate a non-diagnosed cancer, [13] or even lead indirectly to paternity testing.

In the UK, the standard Down Syndrome Screening (DSS) offered through the NHS is also a combined test at 10-14 weeks. It involves a maternal serum marker test and an ultrasound imaging scan.[2] Similarly to Italy and the UK, in China, all women are currently offered Down Syndrome Screening (DSS) through foetal ultrasound scan, combined with maternal serum biomarkers. However, DSS has a false positive rate of 3 - 5% and only 80-90% detection rate [14]. Therefore, an invasive test in the form of amniocentesis or CVS is still required to confirm the positive test. However, there is about 0.5-1% miscarriage risk related to these invasive methods [15]. If the positive result is confirmed at the invasive test, the woman will be advised to go through a post diagnosis counselling process to decide whether to continue her pregnancy or not. However, as we note below, in many countries, including the ones we are analysing, doctors and healthcare professionals do not seem to be adequately prepared to offer genetic counselling for NIPT, including for the possible incidental findings mentioned above.

3. The 'how' is used depends on where is used: market and regulation of NIPT

While the technology underlying NIPT is relatively simple and well-established, the uses of the test differ greatly in the countries we analysed. This is not surprising as how a technology is used is dependent on the cultural, social and political context of each country.

In Italy NIPT is not reimbursed by the SSN (Sistema Sanitario Nazionale, Italian national health system and equivalent of NHS), but is offered privately with a median cost of € 571 (compared to a median price for the combined test of € 104 and median price for invasive cytogenetic test of € 935).[3] As noted above, several regional and national working groups are currently evaluating how NIPT could be included within the SSN However, until clear guidelines are formulated, there is a tangible risk that NIPT can be offered privately by centres that are not competent in performing ultrasound scanning, prenatal diagnosis and genetic counselling pre and post-NIPT.

[2] http://www.nhs.uk/conditions/pregnancy-and-baby/pages/screening-amniocentesis-downs-syndrome.aspx (accessed April 4th, 2016)
[3] http://www.salute.gov.it/imgs/C_17_pubblicazioni_2381_allegato.pdf (accessed April 4th, 2016)

Similarly to Italy and in some ways to Brazil, NIPT is also flourishing in the UK in the private sector, where it is offered for a price about £ 400- £ 700, with results available within two weeks. For these private clinics, ISO 15189 and CE marking certification are the compulsory conditions for providing the NIPT service[4]. However, the implementation of NIPT into the national health system is in sight for 2017/2018, as explained at the end of this section.

In China from 2011 to 201, NIPT prompted the launch of many companies that were offering NIPT testing privately at a commercial price of about 2000-3000 RMB (about £200 - £ 300) in China. In February 2014, after the Chinese commercial market had been offering NIPT for more than three years, the China Food and Drug Administration (CFDA) and the National Health and Family Planning Commission (NHFPC) announced that all genetic testing including NIPT was suspended until new regulation was implemented.[5]. In China, CFDA is responsible for the supervision and administration of medical devices and reagents under the direct supervision state council, while NHFPC has the responsibility to formulate and carry out administrative measures for medical institutions and medical services industry. (http://en.nhfpc.gov.cn/2014-05/07/content_17491484.htm).

Several reasons led to the suspension of NIPT in China in February 2014. The first one was that the expected high benefits of NIPT had already prompted the launch of many companies but, without any regulation in place, CFDA and NHFPC concluded that it was impossible to guarantee that these companies had the capacity to offer clinical testing including NIPT. In other words, the commercial market for genetic testing was perceived to be chaotic with no guarantee that the companies could deliver what they promised. In a the course of a few months in 2014 CFDA worked to strengthen the supervision of genetic testing and produced the regulations for Supervision and Administration of Medical Devices (state council order No. 650), Medical Device Registration Administration Method (CFDA order No. 4), and in vitro diagnostic reagents Registration Administration Method (CFDA order No. 5). Medical Devices and In-vitro Diagnosis have been divided into class I, II and III, taking into account their inherent risks from low to high. According to The Classification for Medical Devices (2002), all reagents and devices for gene testing are under Class III. NIPT belongs to Class III which needs registration examination by CFDA. Between March and May, 2014, BGI (where one of the authors, Zeng, works) had completed 10,598 samples in 20 hospitals and clinical centres in China for clinical validity. BGI submitted the registration of the detection kit for NIPT (T21, T18, T13) (Combinatorial Probe-anchor Ligation Sequencing Method/ Semiconductor Sequencing Method) and the sequencing machines BGISEQ-1000 and BGISEQ-100 for NIPT to CFDA in June, 2014. On June 30th, 2014, CFDA approved BGISEQ-1000 and BGISEQ-100 for medical applications,

[4] ISO 15189: http://www.iso.org/iso/home/store/catalogue_ics/catalogue_detail_ics.htm?csnumber=56115; CE marking: http://ec.europa.eu/growth/single-market/ce-marking/index_en.htm (accessed April 4th, 2016)

[5] http://www.sda.gov.cn/WS01/CL0845/96853.html (accessed April 4th, 2016)

hence BGI received the first certificate for NIPT in China. In the meantime, BGI and China National Institute for Food and Drug control had built up the national reference panel: the DNA reference sequence control materials for sequencing performance evaluation[6]. In January 2015, NHFPC had approved 108 medical institutions as NIPT clinical trial sites. On July 2nd, 2015, NHFPC announced the "Notice of NHFPC on the cancellation of Class III of medical technique clinical application access approval," which means the medical institutions can now offer NIPT without NHFPC's approval.[7]. This does not mean that NIPT has been declassed to class II, but only that NHFPC has changed the regulation rule for class III and the registration of the medical devices and reagents for NIPT in CFDA remains the only condition for a medical institution or a commercial company to provide NIPT to the public.

In December 2015, NIPT was officially included in the handbook of prenatal care of Shenzhen.[8] This was the official recognition that NIPT had been adopted in the public clinical system in Shenzhen, where NIPT is recommended at 14-20 weeks. Pregnant women in Shenzhen pay 880 RMB (about £ 90) for NIPT, with the remaining cost of the test (more than half of the price) being subsided by the Shenzhen government. In some provinces in China, such as Xichuan province and Zhejing province, the Development and Reform Commission has set a price of the NIPT which is proportional to what people earn.

In China, there is no systematic training in genetic counselling: Genetic counsellor is not a professional career and there is no official authentication. Since NIPT is still an advanced and innovative technique, the majority of doctors still lack the appropriate knowledge on how to use it and how to offer appropriate pre- and post-counselling. This is obviously a problem that needs to be addressed. The BGI[9] (where one of the authors, Zeng, works) and NHFPC Talent Exchange Service Center have been pioneers in this sense by holding a series of genetics counselling training courses for doctors in China in 2015. [10]

The situation in Brazil is again different. Abortion is illegal in Brazil for any foetal indication, with the sole exceptions of anencephaly and rape [16]. As a consequence the Brazilian national health system SUS (Sistema Unico de Saude) did not introduce prenatal diagnosis or screening tests to pregnant women. Illegal, however, does not mean rare: one in every five Brazilian women was reported to have an abortion [17]. As the Brazilian physician and author of popular books about medicine Drauzio Varella explained in the context of the debate on risk of induction of foetal malformation by the Zika virus, an abortion for foetal indication is freely accessible in Brazil - for those who can afford it [18]. It means, however, that only affluent women have access to safe abortions [16]. In many

[6] http://www.sda.gov.cn/WS01/CL0051/102239.html (accessed April 4th, 2016)
[7] http://www.nhfpc.gov.cn/yzygj/s3585/201507/c529dd6bb8084e09883ae417256b3c49.shtml (accessed April 4th, 2016)
[8] Shenzhen is the first province in China to have adopted NIPT into the public clinical system.
[9] http://www.genomics.cn/en/index (accessed April 4th, 2016)
[10] http://www.genomics.cn/news/show_news?nid=104519 (accessed April 4th, 2016)

areas, among them gynaecology and obstetrics, middle and upper class women use exclusively private sector services. Brazilian physicians, especially those who work in upper-end private clinics, tend to prescribe numerous complex diagnostic tests, partly as a status symbol: such tests stand for cutting-edge, high quality medicine. For this reason, private Brazilian hospitals often purchase expensive diagnostic equipment such as sophisticated ultrasound and magnetic resonance imagery machines. It is in this private sector that NIPT has flourished in the last three years. Pregnant women treated in the private sector undergo usually some form of screening for Down syndrome risk: usually (similarly to what happens in Italy, UK and China) a combination of a serum test and an ultrasound examination at 11-12 weeks of pregnancy. If these tests uncover a high risk of Down syndrome or another inborn anomaly, the woman usually undergoes an amniocentesis, and if the result is positive, she can chose to have an illegal - but safe - abortion. The low number of children with inborn defects born in private hospital and clinics indirectly attests to the popularity of abortions for foetal anomalies in the private sector [19].

The use of NIPT in Brazil has entered this economy of diagnostic testing through the US. Indeed, US producers of NIPT became very interested in the sizable Brazilian market in 2013, when the US firms Ariosa and Natera signed agreements with Brazilian laboratories and now offer NIPT, together with other blood tests, such as a serum test for Down syndrome risk as part of the clinics 'package deal' of prenatal care.[11] The test is relatively inexpensive; in 2015 its price was around 300-400 reals, that is, approximately $80- $100.

In early 2013, the Brazilian press presented the new test to their readers, with headlines such as, *'Looking for the perfect DNA'*, or *'Blood test which detects Down syndrome arrives to Brazil*.' [20,21]. The latter article explained that NIPT will help families to be better prepared to an arrival of a Down syndrome child, and was illustrated with a photograph of a smiling middle class couple with a cute Down syndrome girl [20]. Down syndrome is systematically presented in Brazilian media as a difference, not a disability, with a strong focus on the blessings of having an 'angel-child' [22-24].

The prescription of NIPT has become dissociated from a calculus of individual risk and became a test that aims to reassure every pregnant woman that her baby is 'all right'. Laboratories that offer NIPT in Brazil took into account this specificity of the local market.

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[11] 'Ariosa Diagnostics and Fleury Group Announce Offering of the Highly Accurate Harmony™ Prenatal Test in Brazil to Assess Risk for Chromosome Conditions in Singleton and Twin Pregnancies', *Ariosa Diagnostic News,* Sept. 12, 2013
http://www.americanownews.com/story/23412770/ariosa-diagnostics-and-fleury-group-announce-offering-of-the-highly-accurate-harmony-prenatal-test-in-brazil-to-assess-risk-for-chromosome-conditions;
DASA Group to Provide Natera's Panorama™ Non-Invasive Prenatal Test for Detection of Chromosomal Abnormalities, Such as Down Syndrome, from the Ninth Week of Gestation, *Business Wire,* August 8, 2013,
http://www.businesswire.com/news/home/20130808005340/en/DASA-Group-Provide-Natera%E2%80%99s-Panorama%E2%84%A2-Non-Invasive-Prenatal (accessed April 4th, 2016)

Gene Laboratorio's advertisement of the Panorama test (produced by Natera), entitled 'Healthy baby, serene pregnancy' explains that there are two versions of the test, a 'conventional' test that detects trisomies 21, 13 and 18, and sex chromosomes anomalies, and an 'amplified' test, which includes also testing for five major chromosomal deletions.[12] The advertisement adds that while Down syndrome is more frequent in older women, the risk of microdeletions does not depend on age: women under thirty are therefore at a higher risk to have a child with a microdeletion than with Down syndrome.[13] The implicit message is that pregnant woman of any age should invest in NIPT to have a 'serene pregnancy'.

Private laboratories such as Centro Paolista de Diagnostica, Pesquisa e Tratamento, or Laboratorio Gene de Belo Horizonte, included in their publicity information about NIPT for Down syndrome. In fall 2013 specialists from private gynaecological clinics were not persuaded that the test would be popular in Brazil. A possible obstacle for its diffusion, they thought, would be its price: approximately 2,000 reals for testing for trisomies 21, 18 and 13 and the foetal sex, non reimbursed by health insurance companies. The price of a serum test for Down syndrome risk (usually PAPP-A test) was 200-300 reals, and of a testing for foetal sex, 300-400 reals. Women could therefore obtain comparable (although less reliable) information at a much lower cost.

One year later, NIPT for Down syndrome became part of the prenatal testing landscape in the Brazilian private health sector. This trend was amplified in 2015. Some professionals explained that they were surprised by the rapidity of adoption of the new technology. Contrary to their earlier suppositions, the price of the test did not seem to discourage affluent women who wanted to be sure their child would not be impaired. Professionals interviewed by one of the authors (Löwy) (not a representative sample) thought also that the uptake of this test was not limited to women over 35 who wished to avoid amniocentesis, and was popular also among young women with very low risk of giving birth to a Down syndrome child. Not infrequently women arrived at their first diagnostic ultrasound examination, conducted at 11-12 weeks of pregnancy, with their NIPT results.

One of the particularities of Brazilian prenatal testing in the past few years is an increasing popularity of ccfDNA based tests exactly for early detection of foetal sex for the middle and upper class women. This test became available in numerous industrialized countries in the first years of the 21 century and was independently elaborated by Brazilian researchers.[25] The test is relatively simple since one does not need next

[12] These deletions are DiGeorge syndrome (22q11deletion, frequency of 1 in 2000 live births), 1p36 deletion syndrome (frequency 1 in 5000) , cri du chat syndrome (5p deletion, frequency 1:20,000), Angleman syndrome (maternal 15q11-13 del, frequency 1 in 12000), and Prader Willy syndrome (paternal 15q11-13 del, frequency in 20,000) .

[13] http://www.laboratoriogene.com.br/exames/nipt-teste-pre-natal-nao-invasivo-em-sangue-materno/ (accessed April 4th, 2016))

generation sequencing (NGS) but it is only looking for something absent in maternal serum, namely markers on the Y chromosomes. There is no patent war on this, and the test is cheap (in 2015 its price was around 300-400 reals, that is, approximately $80- 100). This test has been included from about 2010-11 as part of the package of care in private maternity clinics.

The increasing popularity of this test for sex-determination in Brazil can be explained at least in part by considering that in Brazil knowing the future child's sex and naming her/ him is a key step in integration of the future child into the family. Lilian Krakowsky Chazan described the importance role of learning the foetal sex in their inclusion in the family narrative [26]. Another explanation given by some professionals – but which may be an 'urban legend' and needs to be taken with a pinch of salt - is that women want to know early on the sex of their baby to start shopping for this baby abroad, especially in Florida. It would very interesting to analyse (beyond the scope of this paper) the sociological aspects of cross-contamination between US social rituals of preparations to pregnancy such as 'baby-shower' and how they are translated into a Brazilian context, and what role NIPT testing plays in such rituals.

The difference between China and Brazil in terms of uses of prenatal tests for sex-determination is striking: while in China it is strictly prohibited to use NIPT to determine the sex of the foetus, in Brazil cffDNA test has acquired an increasing popularity. One of the authors is based at BGI, one of the world-largest genomics institutes, in Shenzhen, China. Here, although clinicians have been offering NIPT to detect foetal chromosomal aneuploidies since 2011 (with an interruption in 2014 as explained above) [27], NIPT for sex determination is strictly prohibited according to the population and family planning law of the People's Republic of China with the only exception of parents who are carriers of X-linked inheritable diseases (Article 35: Use of ultrasonography or other techniques to identify foetal sex for non-medical purposes is strictly prohibited. Sex-selective pregnancy termination for non-medical purposes is strictly prohibited.). This prohibition is linked to the fear of selective termination of female foetuses, a fear that is based in the appalling data about the gender ratio in China in the last thirty years. China lacks the intense cultural stigma toward abortion that other countries have [28]. In addition, to control the population in China, the one-child policy was introduced between 1978 and 1980. While the birth rate has dropped dramatically in the last thirty years, the gender ratio at birth increased as a consequence of the policy and cultural preference for male children. Given current trends, it has been estimated that by 2020, there will be approximately 30 million more adult men than adult women. The one-child policy has been recently suspended (October 2015) mostly on grounds of this gender imbalance

The National Institute for Health Research (NIHR) funded RAPID (Reliable Accurate Prenatal non-Invasive Diagnosis), a five-year UK national programme running from 1 Jan, 2009 to 30 Sept, 2015, and aimed at evaluating early NIPD/NIPT based on cffDNA and RNA

in maternal plasma in order to improve the quality of National Health Service (NHS) prenatal diagnostic services. In this study all women undergoing DSS at the eight participating units and who have a risk of >1:1,000 were offered NIPT. RAPID has already provided two positive evaluation reports on NIPT [29, 30]. On January 18th, 2016, the UK National Screening Committee reported evidence based on the RAPID project that NIPT is highly accurate for detection of foetal chromosomal aneuploidies including the detection of trisomy 21, trisomy 18, and trisomy 13, and recommended it for implementation through the NHS to all women. The UK Government now needs to approve the recommendation before it is implemented by the NHS. If the UK Parliament approves the National Screening Committee recommendation (and it is expected that it will), in the near future (2017 or 2018) NIPT could be offered to all women in the UK in substitution of serum test. The news of the recommendation by the UK National Screening Committee to the for implementation through the NHS in substitution of invasive screening has been met with some vocal criticisms by parents of Down syndrome children and other disability rights scholars and activists in the UK.

5. Ethical issues: narrative imaginaries of gender and disabilities

Disability rights scholars and bioethicists have pointed out the potential dangers of increased selective termination of children with Down syndrome resulting from the implementation of NIPT. In particular some scholars have raised the issues that the offer of NIPT would be "irresistible" and would create pressure on women to take the test and terminate the pregnancy in case of a positive result. [31, 32]. Another concern that has been raised by bioethicists in the UK regarding the implementation of NIPT is that, since the test requires only a very simple blood sample, it could lead to the "normalisation", "routinisation" and subsequent "trivialisation" of the screening practice [37], which could lead to selective terminations for similarly "trivial" reasons. However, as noted by Löwy [33], similar earlier 'alarmist predictions' that the liberalization of abortion would lead to the frequent termination of pregnancy for 'trivial reasons', (196), never materialised. We do not think that the rate of therapeutic abortions will increase significantly compared to the pre-NIPT era. The decision to have an abortion is not one that a woman will ever take lightly. Rather, we think that the main effect of the implementation of NIPT will be a significant reduction in the number of useless CVS and amniocentesis. In this sense, the implementation of NIPT will lead to a modulation, and not to a revolution, of the existing landscape of prenatal testing. This will be the case at least in countries such as UK, China or Italy (while that is not the case yet in Brazil, mostly because abortion remains illegal) where all women already undergo some sort of combined 'serum test' and ultrasound scanning for nuchal translucency as a screening for Down Syndrome and other aneuploidies (we note this is not the case, for example, in the US).

As pointed out by one of the authors (Löwy) elsewhere [38], while technologies are initially shaped by the values and preferences of people who develop them" they can later "be modified by their users". (p. 202) For example, amniocentesis was first introduced in the 1950s to look at blood type of the foetus and save the foetus in case of maternal-foetal Rhesus factor incompatibility, not for prenatal screening [34]. Something similar, as shown in this paper, is already happening in Brazil, where NIPT is becoming the 'status symbol' of those who can afford an extra package for their children, to demonstrate how wanted their child is, and how welcomed to the family it is. An upper class woman in Brazil can indeed see NIPT as a good, not a 'frivolous' investment for 'trivial reasons'. Services provided by the high-end maternity clinics are usually not reimbursed by Brazilian health insurances. Women who chose such clinics because of their reputation of excellence are already ready to pay important sums of money from their pocket for quality prenatal care. The price of NIPT (in 2016) was not very high when compared to their other health-related expenses. In a sub-culture that puts to the fore the consumerist aspect of health care and of maternity, purchase of a non-invasive prenatal tests may be seen as a less frivolous version of purchase of a luxurious baby pram. In Brazil, NIPT has become smoothly integrated into a high tech supervision of pregnancy accessible to affluent women, which includes testing for foetal anomalies and (illegal) abortions for such anomalies.

Australian philosopher and author of Futures of Reproduction (2011) Catherine Mills has written about the power of imaging technologies in bestowing moral status of the foetus or "performing personhood" [34-36] with ambiguous results depending on the context and lived experience of pregnancy: it makes a difference whether the imaging technology is used as in some US states to discourage women from selectively terminating a pregnancy, or if imaging is sought by women and family as a visual narrative that can anticipate the unborn person and prepare its acceptance into the world.[36] As described above, our data on the use of NIPT in Brazil show that, in a similar way to when it is used for sex determination, NIPT can be used to detect trisomy 21 and prepare the couple for the arrival of the child affected by Down syndrome. In this sense, NIPT testing pairs with imaging technologies to create and anticipate the expectation of the future child, which through the technology acquires the status of future child and member of the family. This is valid both to detect Down syndrome children and for sex determination. As the narrative of the Down syndrome child in Brazil is very pervasive, the trait is not necessarily seen as a disability but as a difference to be welcomed. The cognitive health impairments are not necessarily perceived as something to 'get rid of' as they are seen to be linked with desirable qualities of Down syndrome identity, such as compassion, generosity and openness. It is therefore possible to speculate that NIPT would not necessarily trigger a selective termination in case of a positive result, although we do not have data to support this hypothesis. Hence we recommend that empirical data on the uptake of NIPT and the

decisions taken by women as a result of a positive test are collected following the implementation of NIPT through NHS in UK, Italy or in specific provinces in China (as we mentioned above, it is unlikely that NIPT will be offered through SUS in Brazil).

We should also like to comment on the striking difference between China and Brazil in terms of uses of NIPT for sex-determination: while NIPT gained increasing popularity for sex determination in Brazil with the upper-middle class, in China it is strictly prohibited to use NIPT to determine the sex of the foetus. This is due to the fact that while in China there is a strong evidence of preference for boys over girls and evidence of selective-termination which led to a disparity in sex ratios over the past thirty years, in Brazil all the interrogated health professionals agreed that they do not have strong preference for boys, and that it is highly unlikely that a woman will abort a female foetus. In China, as Down Syndrome Screening already exists in the public health system and is linked to the possibility of selective termination; it does not seem plausible to speculate that the implementation of NIPT on a wide scale would increase the rate of abortion. In China, the main reasons for abortion are likely to remain linked to sexual discrimination, even with the current suspension of the one-child policy (families who have one female child may try to have a second male child to continue their heritage).

Other issues that seem to us to deserve ethical attention pertain to how to deal with possible incidental findings resulting from a maternal chromosomal mosaicisms due to an anomalous (possibly cancerous) cellular line, and other hidden abnormalities in one of the parents, including genetic diseases with late expressions in life [11]. The counselling step following a positive result will be of the utmost importance. As highlighted above, in China doctors are not trained in genetic counselling. In Italy the genetic counselling is included in the NIPT fee, i.e. if the NIPT results show high risk, the private company will offer to the couple genetic counselling without charging any additional cost. In Brazil some high-end clinics provide genetic counselling for women who test 'positive' but this is at the discretion of the woman's doctor - and of course the woman has to pay for this service. But as we have noted above, as long as NIPT is offered by private companies and not through the national health system, there is a tangible risk that it can be offered by centres that are not competent in performing ultrasound scanning, prenatal diagnosis and genetic counselling pre and post-NIPT.

6. Conclusions

Contrary to what others have argued, this paper has shown that in the immediate future we think that NIPT will be limited to 'modulating', not drastically changing or

revolutionising, the use of existing diagnostic approaches, at least in the countries we analysed (the US situation is different).

However, we note how in the more distant (but not too far ahead!) future the impact of the NIPT technology will be different, as researches such as Whole Genome Sequencing (WGS) analysis based on NIPT are ongoing [39] and it is plausible to speculate that in the future WGS will be offered in conjunction to NIPT. Future evolutions of NIPT combined with whole genome sequencing (WGS) will make the foetus even more accessible to that 'medical gaze' that has been already drastically changed the meaning of pregnancy for millions of women since the introduction of ultrasound scanning with the emergence of foetal images. [34, 36] NIPT testing needs to be positioned within this trajectory of prenatal diagnosis that, as argued by Löwy, "displays the role of conflicting values (and often incommensurable moral economies) in the emergence of new technologies, and in their transformation into routine medical procedures" [38, 187]. The two 'often incommensurable moral economies' are women's autonomy and individual-centred medicine, as emphasised in gynaecologists and midwives/obstetricians' public discourse; and considerations about the cost/efficacy of long-term care for people with Down Syndrome or other chromosomal-related disabilities as emphasized in public health discourses.

These two contrasting narratives are also at play (more or less covertly) in the discourses around NIPT. It seems to us that bioethics scholarship has failed to engage thus far with the ethical issues that arise at the nexus of these conflicting values and moral economies, as it has focused only on the former framing, and discussion of possible conflicts between women's rights to self-determination and autonomy and children's future rights; or on the latter framing and the disability rights critiques to the screening. It is important that bioethics scholarship engages proactively with the ethical issues that arise at the nexus of these conflicting values and moral economies. Such an engagement would lead shift the focus of the ethical analysis from questions such as ""In what ways is it ethically acceptable to use NIPT?" to: "In what ways will the implementation of NIPT through the NHS change the ways in which women think about their pregnancy?", and "In what ways will women be held responsible for the types of pregnancies they decide to carry?" among others, and to seriously engage with socio-ethical issues created by upstream, top-down decisions on implementation of a technology. NIPT coupled with WGS will lead to a completely new level of 'supervision', 'management' and 'scrutiny' of human foetuses and pregnant women, that we have a responsibility to start discussing now, taking into account first and foremost the voices of the pregnant women.

REFERENCES

1. Allyse M, Minear MA, Berson E, Sridhar S, Rote M, Hung A, et al. Non-invasive prenatal testing: a review of international implementation and challenges. Int J Womens Health 2015; 7 :113-26.

2. Lo YM, Corbetta N, Chamberlain PF, Rai V, Sargent IL, Redman CW, et al. Presence of fetal DNA in maternal plasma and serum. Lancet 1997; 350:485–7.

3. Chiu RW, Chan KC, Gao Y, Lau VY, Zheng W, Leung TY, et al. Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. Proc Natl Acad Sci USA 2008; 105:20458–63.

4. Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. Proc Natl Acad Sci USA 2008; 105:16266–71.

5. Medda E1, Donati S, Spinelli A, Di Renzo GC; EUROPOP Group Czech Republic; EUROPOP Group Finland; et al. Genetic amniocentesis: a risk factor for preterm delivery? Eur J Obstet Gynecol Reprod Biol 2003; 110:153-8.

6. Wilson KL, Czerwinski JL, Hoskovec JM, Noblin SJ, Sullivan CM, Harbison A, Campion MW, Devary K, Devers P, Singletary CN. SNGC practice guideline: prenatal screening and diagnostic testing options for chromosome aneuploidy. J Genet Couns. 2013; 22(1): 4-15

7. Bianchi DW, Parker RL, Wentworth J, Madankumar R, Saffer C, Das AF, et al. Care study group: DNA sequencing versus standard prenatal aneuploidy screening. N Engl J Med 2014; 370: 799-808.

8. Dan S, Wang W, Ren J, Li Y, Hu H, Xu Z, et al. Clinical application of massively parallel sequencing-based prenatal noninvasive fetal trisomy test for trisomies 21 and 18 in 11,105 pregnancies with mixed risk factors. Prenat Diagn 2012; 32:1225-32.

9. Gil MM, Quezada MS, Bregant B, Ferraro M, Nicolaides KH. Implementation of maternal bold cell-free DNA testing in early screening for aneuploidies. Ultrasound Obstet Gynecol 2013; 42:34-40.

10. Song Y, Liu C, Qi H, Zhang Y, Bian X, Liu J. Noninvasive prenatal testing of fetal aneuploidies by massively parallel sequencingin a prospective Chinese population. Prenat Diagn 2013; 33: 700- 6.

11. Bianchi DW, Chudova D, Sehnert AJ, Bhatt S, Murray K, Prosen TL, et al. Noninvasive prenatal testing and incidental detection of occult maternal malignancies. JAMA 2015; 314: 162-9.

12. Curnow KJ, Wilkins-Haug L, Ryan A, Kırkızlar E, Stosic M, Hall MP, et al. Detection of triploid, molar, and vanishing twin pregnancies by a single-nucleotide polymorphism–based noninvasive prenatal test. Am J Obstet Gynecol 2015; 212: 79.e1-9.

13. Osborne CM, Hardisty E, Devers P, Kaiser-Rogers K, Hayden MA, Goodnight W, et al. Discordant noninvasive prenatal testing results in a patient subsequently diagnosed with metastatic disease. Prenat Diagn 2013;33:609-11.

14. Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn. 2011; 31:7-15.

15. Tabor A, Alfirevic Z. Update on procedure-related risks of prenatal diagnosis techniques. Fetal Diagn Ther 2010; 27:1-7.

16. Diniz D, Medeiros M. Abortion in Brazil: a household survey using the ballot box technique. Cien Saude Colet 2010;15:959-66.

17. Mirlesse , *Diagnostic prénatal et médecine fœtale. Du cadre des pratiques à l'anticipation du handicap. Comparaison France –Brésil*, unpublished PhD thesis in public health, University of Paris XIII, 2014.

18. Drauzio Varella" BBC Brazil, 2.2.2016. http://www.bbc.com/portuguese/noticias/2016/02/160201_drauzio_aborto_rs

19. Horovitz, Dafne Dain Gandelman, Victor Evangelista de Faria Ferraz, Sulamis Dain and Antonia Paula Marques-de-Faria, Genetic services and testing in Brazil, Journal of Community Genetics, 2013, 4: 355–375.

20. Fábio Rossi, 'Em busca do DNA perfeito, *O Globo*, 23.2.13 http://oglobo.globo.com/sociedade/saude/em-busca-do-dna-perfeito-7654646

21. Luna D'Alama, 'Exame de sangue que vê síndrome de Down em feto chega ao Brasil', *O Globo*, 23.1.2013. http://g1.globo.com/bemestar/noticia/2013/01/exame-de-sangue-que-ve-sindrome-de-down-em-feto-chega-ao-brasil.html

22. Cardoso, Maria Helena Cabral de Almaida, A herança arcaica de um modelo: história, medicina...e a Síndrome de Down, unpublished PhD thesis, Instituto Fernandez Figueira, Fiocruz, 2000.

23. Cardoso MH. Production of meanings related to Down syndrome. Cad Saude Publica 2003; 19:101-9.

24. Gilbert, Ana Cristina Bohrer, Vertice do Impensável: um estudo de narrativas em síndrome de Down, Rio de Janeiro, Editora Fiocruz, 2012 (book).

25. Martinhago CD, de Oliveira RM, Tomitão Canas Mdo C, Vagnini LD, Alcantara Oliveira JB, Petersen CG, et al. Accuracy of foetal gender determination in maternal plasma at 5 and 6 weeks of pregnancy. Prenat Diagn 2006; 26:1219-23.

26. Lilian KC. É... tá grávida mesmo! E ele é lindo!'A construção de 'verdades' na ultra-sonografia obstétrica. *Manguinhos* 2008; 15: 99-116.

27. Zhang H, Gao Y, Jiang F, Fu M, Yuan Y, Guo Y, et al. Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical e xperience from 146 958 pregnancies. Ultrasound Obstet Gynecol 2015; 45: 530–8.

28. Schiavenza M. Today's China statistic: abortions. The Atlantic, 19 March, 2013.

29. Hill M, Wright D, Daley R, Lewis C, McKay F, Mason S, et al. Evaluation of non-invasive prenatal testing (NIPT) for aneuploidy in an NHS setting: a reliable accurate prenatal non-invasive diagnosis (RAPID) protocol. BMC Pregnancy Childbirth 2014; 14:229.

30. Chitty L, Cameron L, Daley R, Fisher J, Hill M, Jenkins L, et al. RAPID Non-invasive prenatal testing (NIPT) evaluation study Executive summary 2015.

31. Kaposy C. A disability critique of the new prenatal test for Down syndrome. Kennedy Inst Ethics J 2013; 23:299-324.

32. Kaposy C. A personal experience of prenatal testing for Down syndrome. Narrat Inq Bioeth 2013; 31:18-21.

33. Löwy I. "Prenatal diagnosis: The irresistible rise of the 'visible foetus'. Stud Hist Philos Biol Biomed Sci. *2014;* 47: 290-29.

34. Mills C. Futures of reproduction: Bioethics and biopolitics. *Springer Science & Business Media* 2011; 49.

35. Mills C. Symposium on 'after-birth abortion': The performativity of personhood. *Monash bioethics review* 30 2012; 1: 61-64.

36. Mills C. Making foetal persons: Foetal homicide, ultrasound, and the normative significance of birth. *philoSOPHIA* 4 2014; 1: 88-107.

37. Deans, Zuzana, Angus J. Clarke, and Ainsley J. Newson. "For Your Interest? The Ethical Acceptability of Using Non-Invasive Prenatal Testing to Test 'Purely for Information'." *Bioethics* 29, no. 1 (2015): 19-25.

38. Löwy I. "Norms, values and constraints. The case of prenatal diagnosis" in Isabelle Dussauge, Claes-Fredrik Helgesson, and Francis Lee (eds) Value Practices in the Life Sciences and Medicine, Oxford UP; 2015, 186-204..

39. Lo YM, Chan KC, Sun H, Chen EZ, Jiang P, Lun FM, et al. Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus. Sci Transl Med 2010; 261:61ra91.